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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/888,824	06/25/2001	Eric Perrier	11123.24US01	9749

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EXAMINER	
HANLEY, SUSAN MARIE	

ART UNIT	PAPER NUMBER
1651	

MAIL DATE	DELIVERY MODE
09/21/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/888,824	PERRIER ET AL.	
	Examiner	Art Unit	
	Susan Hanley	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *70,72-78,82-86,91,96 and 98-100* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *91* is/are allowed.

6)☒ Claim(s) *70,72-78,82-86,96 and 98-100* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/16/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 5/16/07 has been entered.

Claims 70, 72-78, 82-86, 91, 96 and 98-100 are presented for examination.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 70, 72, 76, 78, 82, 85, 86, 96 and 98-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Comai et al. (US 4,218,443; cited in the IDS filed 8/31/04) in view of Guegler et al. (US 2002/0052034; new reference), Nozaki et al. (1984; new reference), Taber's Medical Dictionary (new reference) and Wang et al. (cited in the Office action of 4/1/06).

Comai discloses an *in vitro* cell-free method for determining if ionophores are inhibitors of LPL and suitable for anti-obesity and hypotriglyeridemic agents in warm blooded agents. Comai discloses that acetone powders of rat epididyml adipose tissue were obtained from homogenized adipose tissue. After filtration, the extract was washed with acetone and ethyl ether and then

dried under vacuum (col. 19, lines 47-65). "The lipoprotein lipase was extracted from the acetone powder into 0.05 M NH_4OH-NH_4Cl buffer" (lines 64-65). Applicant is particularly directed to col. 19, lines 51-52 which refer to their preparation as the "separation of molecular species of lipoprotein lipase from adipose tissue." This disclosure establishes that the LPL used for the assay is separated from cells and cell lysates since the LPL was transferred from the homogenate into the NH_4OH-NH_4Cl buffer.

The activity of the LPL was determined by combining the LPL with the substrate, ^{14}C-labelled glycerol trioleate (triolein, as in instant claims 78 and 82), lysophosphatidylcholine, bovine serum albumin, the fatty acid sequestering agent, (as in instant claim 76) and fasted rat serum. The liberated ^{14}C-labelled free fatty acids were extracted into a carbonate buffer and the radioactivity was quantified. The ionophores were added as solutions in water or DMSO to the assay and LPL inhibition was measured. Thus, LPL was measured in the presence and absence of the inhibitor, as in instant claim 72. The ionophore inhibitors were also tested *in vivo* to determine their ability to inhibit lipolysis and effect weight loss (col. 20, lines 3-48). Thus, Comai establishes that an *in vitro* cell-free or cell-free lysate is used to assay inhibitors that inhibit LPL for the purpose of determining compounds suitable for therapeutic compositions that limit the uptake of fatty acids by adipocytes *in vivo* in order to reduce obesity and hyperlipidemia.

Comai does not teach that the release of fatty acids is enzymatic, the addition of a human colipase or explicitly disclose that such an in vitro assay can be employed to screen for inhibitors of lipolysis suitable for therapeutic purposes.

Guegler establishes that lipases, and lipoprotein lipase in particular, are central to lipolysis and control the balance of free fatty acids in adipose tissue (section 006-009). Guegler teaches

that agents that modulate lipases can be identified using cell-based or cell free system first and then confirm activity in an animal or other model system. Such model systems are well known in the art and can readily be employed in this context (section 0067). Modulators of lipase protein activity identified according to these drug screening assays can be used to treat a subject with a disorder mediated by the lipase pathway by treating cells or tissues that express the lipase (section 0066).

Nozaki discloses an in vitro cell-free enzymatic method for measuring LPL activity in post-heparin plasma that is equivalent to determining LPL activity via a radiometric assay. The measurement is carried out by preparing the substrate, triolein, in an emulsion and adding BSA as the fatty acid acceptor. The enzyme LPL which is obtained from post-heparin plasma is added and the mixture incubated. Taber's Medical Dictionary teaches that plasma comprises the liquid part of lymph and of the blood and contains water, electrolytes, sugars, proteins, fats, gases, bile pigments, etc. (Taber's, p. 1313). Thus, plasma lacks cells and LPL obtained from post-heparin plasma is in a cell-free environment. Free fatty acids are extracted via Triton X-100. A NEFA Kit-K is used to measure the FFA by employing acyl-CoA synthetase, acyl CoA oxidase and peroxidase to react with free fatty acids to produce a change in OD at 550 nm in order to determine the concentration of non-esterified fatty acids in a sample. This disclosure meets the limitations of claim 70, part c) that requires measurement by an enzymatic method, and claims 85-86 that require an optical density measurement at 550 nm to determine FFA and LPL activity. Nozaki discloses that the enzymatic method has the advantage in that the method directly measures the extracted free fatty acids without any influence of triglycerides, which is a problem in the radiometric method. The enzymatic method does not require radioisotopes which require special equipment and handling (p. 740, see the disclosure under the "Discussion" heading).

Wang et al. disclose that optimal LPL assay conditions for the hydrolysis of long chain triacylglycerols requires the combination of bovine serum albumin with apoC-II colipase because they act synergistically for the preferential activation of long chain substrates. A long chain substrate includes C-18 (triolein) (abstract).

It would have been obvious to one of orindary skill in the art at the time the invention was made to employ a cell-free enzymatic assay, as taught by Nozaki, instead of a radiometric method to screen inhibitors of LPL to determine their potential to limit the uptake of free fatty acids by adipocytes. The ordinary artisan would have been motivated to do so because Guegler establishes that cell-free lipase assays are well-known for screening potential modulators of free fatty acid levels for pharmacological purposes. Furthermore, Nozaki teaches that the cell-free enzymatic method is comparable to the cell-free radiometric method in terms of accuracy. Nozaki also discloses that the enzymatic method directly measures the free fatty acids and that the non-radiometric assays do not require special equipment or problem of the disposal of radioactive waste. The ordinary artisan would have had a reasonable expectation that inhibition of LPL by the ionophores of Comai could be reliably determined by the method of Nozaki and the NEFA kit because the kit is in commercial use and employs a chain of enzyme reactions that are known to produce a reliable change in OD at 550. The ordinary artisan would also have had a reasonable expectation that inhibitors of LPL identified by a cell-free enzymatic assay would be candidates to regulate free fatty acids levels in adipocytes because Guegler teaches this physiological relationship and ties it to the screening of lipase inhibitors.

The ordinary artisan would have been motivated to add apoC-II colipase to the assay mixture because it acts synergistically with BSA, which is present in Comai's assay mixture, to

optimize assay conditions for long chain triglycerides such as triolein which is employed in the Comai assay. The ordinary artisan would have had a reasonable expectation that the addition of apoC-II colipase to the reaction mixture of Comai would be successful because Wang demonstrated that the combination of apoC-II colipase and BSA causes a shift of LPL longer chain triglyceride substrates.

Thus, Comai in view of Guegler and Nozaki clearly teach that the ordinary artisan would have known that one could identify inhibitors of LPL intended for therapy to limit the uptake of fatty acids by adipocytes by an *in vitro* cell-free or cell-free lysate assay. However, the combined disclosures do not teach specifically teach using an *in vitro* cell-free or cell-free lysate to assay for LPL inhibitors that can be used in a topical composition or for stimulating microcirculation. These limitations have not been given patentable weight because, the although the recitation occurs in the preamble and the body of the claims, the limitation only recites the purpose of a process and the actual steps of the claims do not depend on either phrase for completeness but, instead, the process steps are able to stand alone. Even if one were to give the phrases patentable weight, the combined disclosures teach the claimed assay. Thus, any compound identified by the assay is suitable for a topical composition or to stimulate microcirculation because the identified compound can inhibit LPL and thus cause the reduction in size of adipocytes which is the desired therapeutic effect. "The structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made, or where the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product." See, e.g., In re Garnero, 412 F.2d 276, 279, 162 USPQ 221, 223 (CCPA 1979).

Claims 70, 72, 76-78, 82, 85, 86, 96, and 98-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Comai et al. (US 4,218,443; cited in the IDS filed 8/31/04) in view of Guegler et al. (US 2002/0052034; new reference), Nozaki et al. (1984; new reference), Taber's Medical Dictionary (new reference) and Wang et al. (cited in the Office action of 4/1/06), as applied to claims 70, 72, 76, 78, 82, 85, 86, 96 and 98-100, in further view of Vanio et al. (1982; "Vanio").

The combined disclosures by Comai, Guegler, Nozaki, Taber's and Wang (1993) are discussed *supra.*

The combined disclosures do not disclose the use of a colipase that is apoC-II colipase from a human source, the use of LPL from a bovine milk source or the additional steps of instant claim 83.

Vanio discloses that LPL requires apoC-II colipase for maximal activity. ApoC-II is a protein component of the surface film of both chylomicrons and VLDL in the *in vivo* substrates of LPL (p. 387-388. bridging paragraph). Vanio teaches an assay for LPL activity wherein the source of the purified LPL was bovine milk while the apoC-II colipase was human VDL. The cell-free assay was carried out by reacting the radio-labelled triolein substrate in a mixture containing BSA and heparin with the LPL (p. 387, left column). Thus, Vanio establishes that apoC-II colipase has two *in vivo* functions: to activate LPL *in vivo* as well as serving as part of the complex comprising the *in vivo* substrate.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ LPL isolated from bovine milk and human apoC-II in the assay disclosed by the combined references as well as adding the steps of instant claim 83. The ordinary artisan would have been motivated to use LPL isolated from bovine milk in the assay taught by the combined

references because it appears to be interchangeable with human LPL. The ordinary artisan would have come to this conclusion because Vanio employs bovine milk LPL with apoC-II colipase from a human source. Given that it was known at the time the colipase was an activator of LPL, the employment of an enzyme and colipase from different species suggests that the sources of the LPL and colipase are not critical to the assay.

The ordinary artisan would have been motivated to incubate apoC-II colipase with LPL and the substrate prior to combining the LPL and the substrate because apoC-II colipase is known to interact with LPL and the substrate *in vivo*. The ordinary artisan would have realized from Vanio the importance of mimicking the *in vivo* lipolytic conditions. The ordinary artisan would have had a reasonable expectation that the apoC-II colipase could be incubated with the LPL and substrate before the combination of said LPL and substrate because the association of LPL and the substrate occurs *in vivo*.

Claims 70, 72-78, 82-86, 96, and 98-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Comai et al. (US 4,218,443; cited in the IDS filed 8/31/04) in view of Guegler et al. (US 2002/0052034; new reference), Nozaki et al. (1984; new reference), Taber's Medical Dictionary (new reference), Wang et al. (cited in the Office action of 4/1/06), and Vanio et al. (1982), as applied to claims 70, 72, 76-78, 82, 85, 86, 96, and 98-100, in further view of Kobayashi (US 3,875,007).

The combined disclosures by Comai, Guegler, Nozaki, Taber's , Wang (1993) and Vanio (1993) are discussed *supra*.

The combined disclosures do not disclose that the activity of an inhibitor is compared to the effect of a compound known to inhibit LPL activity, wherein the compound is protamine sulfate, protamine or sodium pyrophosphate.

Kobayashi discloses that the lipolytic activity of a substance designated as GA-56 was established, in part, by comparing the activity of known inhibitors of LPL on its activity. The known LPL inhibitors included protamine sulfate. None of the known LPL inhibitors had any effect on the lipolytic activity of GA-56. Kobayashi concluded that GA-56 was not a like known LPL's (Table I).

It would have been obvious to one of ordinary skill in the art to compare the activity of an experimental inhibitor with that of a known LPL inhibitor. The ordinary artisan would have been motivated to do so because the comparison provides information regarding the ability to inhibit LPL activity compared to a known quantity.

The following references are cited to further establish the state of the art:

Kubo et al. Biochim. Biophys. Acta (1987) 918: 168-174.

Jong et al. Biochem. J. (1997) 328: 745-750.

de Man et al. Atherosclerosis. (1998) 136: 255-262.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Hanley whose telephone number is 571-272-2508. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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